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REVIEW ARTICLE

Systematic literature review: xerostomia in advanced cancer patients

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Abstract
Purpose Dry mouth (xerostomia) is one of the commonest symptoms in cancer patients and can adversely affect quality of life. The aim of this review was to determine the effectiveness of pharmacological and non-pharmacological interventions in treating xerostomia in adult advanced cancer patients.
Methods The literature search was performed in February 2014 using databases including EMBASE, MEDLINE, CINAHL, BNI and Cochrane library. The search was carried out using standard MeSH terms and was limited to adult population and English language. Studies investigating xerostomia secondary to head and neck cancer treatment and autoimmune disease were excluded. Titles and abstracts were screened and reviewed for eligibility. Only studies involving primary research were included in the analysis.
Results Six studies met the eligibility criteria for review: three randomized controlled trials and three prospective studies. The quality assessment and reporting was performed using PRISMA, Jadad and STROBE. These studies compared acupuncture, pilocarpine, Saliva Orthana and chewing gum with each other or with placebo. All interventions were considered effective in treating xerostomia. However, effectiveness versus placebo could not be demonstrated for Saliva Orthana. Meta-analysis could not be performed due to heterogeneity of the study type and intervention.
Conclusion Limited published data exists reporting the effectiveness of measures in the treatment of xerostomia in cancer patients. Based on primary research of low quality, firm conclusions cannot be drawn. However, pilocarpine, artificial saliva, chewing gum and acupuncture can be tried based on the available data. This highlights the explicit need to improve our evidence base. Properly constructed randomized controlled trials demonstrating effectiveness of pharmacological and non-pharmacological interventions for dry mouth are required.

Keywords Xerostomia · Pilocarpine · Artificial saliva · Advanced cancer

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Introduction

Xerostomia is the subjective experience of dry mouth and can be associated with reduced salivary gland flow [1]. Reduced salivary flow can in turn lead to increased risk of oral fungal infection, caries, swallowing problems and altered taste [2, 3]. Xerostomia is a common symptom in patients with advanced cancer with prevalence reported of up to 77 % of hospice admissions [4]. Advanced cancer is defined as that which is incurable but is still amenable to life prolonging treatment [5]. Causes in this patient group are numerous and include the consequences of the cancer itself; dehydration and general debility; the effect of cancer treatments; concomitant use of medications such as opioids, antimuscarinics and diuretics and pre-existing comorbidities such as Sjogren's syndrome [6].

Patients report xerostomia as a distressing symptom with significant impact on the quality of life [7]. Initial aims of management should be to identify the primary cause and treat reversible causes where possible. A clear drug history and review is required. Examination of the mouth is important to identify any fungal infection. If further symptomatic relief is required, treatment is divided into non-pharmacological and pharmacological measures. Drug treatments are grouped as salivary substitutes or salivary stimulants. Non-pharmacological examples include mouth care, ice cubes

and chewing gum [8]. Artificial saliva is a salivary substitute and is considered a poor substitute for natural saliva [9]. Salivary stimulants should increase flow if the salivary glands are intact [10].

Systemic pharmacological treatments include parasympathomimetic agents such as pilocarpine and bethanechol that act on β-adrenergic receptors and stimulate secretion from salivary glands. In clinical practice, they are used to treat xerostomia after radiotherapy for head and neck cancer [9] but are associated with side effects such as headache and sweating [11]. The effects of many pharmacological and non-pharmacological interventions such as pilocarpine and acupuncture have been assessed in several studies in patients with radiotherapy-induced xerostomia (head and neck cancer patients) and in graft versus host disease.

The peer-reviewed survey performed by our research group found that xerostomia is a major problem in palliative care patients, and none of the interventions currently used were regarded to be effective or very effective [12]. A recently published cross-sectional study in cancer patients reported that xerostomia received the second highest mean score on a modified Edmonton Symptom Assessment Scale (ESAS) after fatigue [13]. Despite a high prevalence and clear impact on patients' quality of life, there is poor recognition of the effect of xerostomia and a lack of evidence regarding the effective management of this condition. This review explores the evidence for interventions in dry mouth in advanced cancer patients excluding those with treatment for head and neck cancer.

Objectives

The objective of this review was to determine the effectiveness of various pharmacological and non-pharmacological measures in relieving the symptom of xerostomia in patients with advanced malignancy.

Methodology

We initially performed a scoping search to identify interventions used in management of xerostomia to inform the subsequent literature search (Table 1).

Selection of literature

A literature search was carried out on 25 February 2014 using MEDLINE (1966–February 2014), EMBASE (1980–February 2014), CINAHL (1982–February 2014), BNI and Cochrane using the MeSH term by the librarian, as detailed in Table 1.

Table 1 Description of MeSH terms used for literature search

	MeSH terms (applied to MEDLINE, EMBASE, CINAHL, BNI, Cochrane)
Population	Cancer OR oncolo* OR maligna* OR palliat* OR neoplas*OR tumour. OR 'terminal care'. OR Hospice*
Intervention	Pilocarpine OR bethanechol OR parasympathomimetic OR muscarnic OR salagen OR myotonine Artificial saliva OR Bioxtra OR Glandosane OR Biotene gel OR Oro balance gel OR Saliva Orthana OR salivix pastilles 'chewing gum' OR 'ice cubes' OR 'mouth care' OR pineapple OR 'boiled sweets' OR citrus OR Acupuncture
Outcome	Dry mouth OR xerostomia OR hyposalivation OR salivary gland dysfunction

The population addressed by the review included adult advanced cancer patients who suffered from xerostomia. The search was limited to adults (age >18) and English language articles. All recognized pharmacological interventions and non-pharmacological interventions were included in the search strategy. Titles and abstracts were screened and reviewed for eligibility. Patients with head and neck cancer who had radiotherapy or surgery, or those with autoimmune diseases or graft versus host disease were excluded. This was considered as a different population with direct effect on salivary gland function either due to disease or its treatment. Xerostomia as a consequence of radiotherapy is most often due to a permanent salivary gland hypofunction but in other cancer patients the cause of xerostomia could be different and multifactorial [14].

Only primary research articles were included in the final analysis and review articles were excluded.

Data collection and analysis

The inclusion and exclusion criteria were decided a priori (Fig. 1). A total of 904 references were identified and 218 duplicates were removed. Forty-two articles remained following application of the eligibility criteria for studies. The PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart (Fig. 1) shows the methodology used to select the final six primary research articles including eligibility criteria for selected studies.

Two review authors, using data extraction forms devised by the research team, read all six selected articles independently. These forms were compared and any differences in interpretation resolved by consensus and in consultation with a third review author. Data analysis and comparison between studies by meta-analysis was not possible due to the heterogenic nature of the included studies.

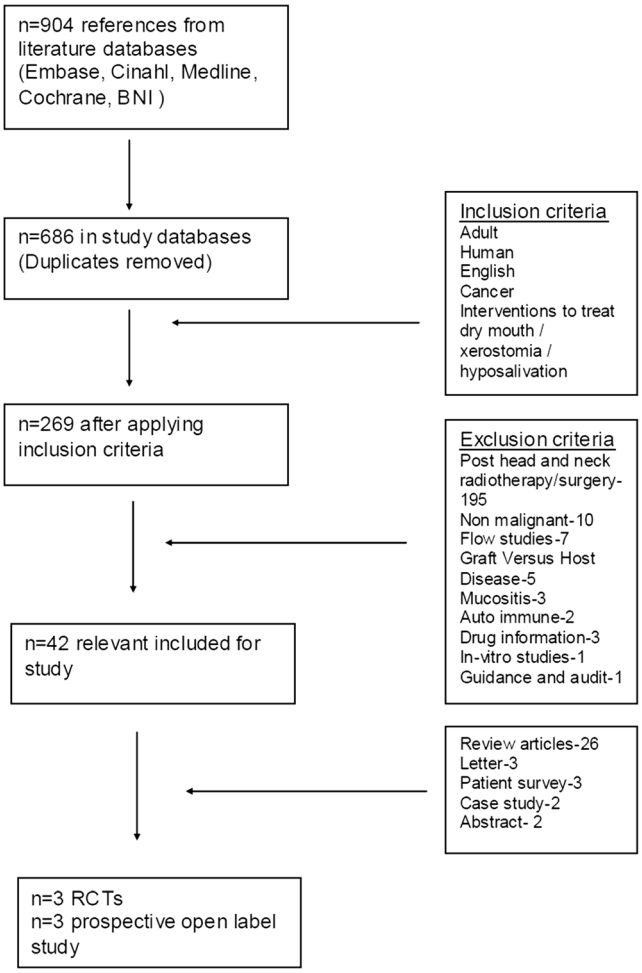

Fig. 1 PRISMA flow chart to demonstrate the methodology applied to select articles

Relevant studies included for this review were quality scored using the Oxford quality scale [15], a five-point scoring scale that assesses methods of randomization and blinding. The prospective studies were reviewed using the STROBE statement (Strengthening The Reporting of Observational Studies in Epidemiology) [16].

Results

Participant characteristics

A total of 198 participants entered and 120 completed the studies. All but four participants had advanced cancer with xerostomia. Three studies mentioned radiation-induced xerostomia as their exclusion criteria [17–19]. The two acupuncture studies mentioned limited exclusion criteria: clotting disorders [20] and estimated prognosis of less than 5 weeks [21]. Sweeney et al. did not mention exclusion or inclusion criteria [22].

Study design

Six studies were included in the final review: two crossover studies, one double-blind, single-phase, placebo-controlled trial and three prospective studies. All studies were performed using different interventions including Saliva Orthana (artificial saliva), chewing gum, pilocarpine and acupuncture. Table 2 summarizes the design of the studies, interventions and outcomes.

Description of studies

Artificial saliva versus pilocarpine

A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer [18] This 5-week crossover study compared a mucin-based artificial saliva (Saliva Orthana™) with pilocarpine hydrochloride (Salagen™) 5 mg three times a day. The participants received 2 weeks of one treatment, a washout period of 1 week and then 2 weeks with the alternating treatment. Treatments were randomly allocated.

This trial showed a greater improvement, which was statistically significant, in the xerostomia visual analogue scale (VAS) scores for pilocarpine compared to Saliva Orthana ($p<0.003$), quoted as +42 and +12 %, respectively. The authors noted a 'treatment period' interaction with a significant carry-over effect with pilocarpine. Data from only the first phase of the study was analysed to determine the effectiveness of treatments, but data from both phases was used to assess the participants' overall experience about the treatment. Some participants withdrew from study because of side effects with pilocarpine ($n=9$) and Saliva Orthana ($n=3$). Only 26 participants had both treatments, with half of these wanting to continue pilocarpine due to efficacy, and half preferring Saliva Orthana, because it was available in a spray and avoided addition to tablet burden.

Artificial saliva versus chewing gum

A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer [17] This prospective, randomized, open, crossover study compared mucin-based artificial saliva (Saliva Orthana™) with a low tack, sugar-free chewing gum (Freedent™). Participants were randomly allocated to receive 5 days of one treatment, have 2 days washout and then 5 days of alternative treatment. They were asked to use the product four times a day (before breakfast, lunch, dinner and bedtime) and other times if necessary.

This study demonstrated modest improvements in xerostomia VAS scores (+22 mm for artificial saliva and + 30 mm for chewing gum). Overall, the majority of participants

Table 2 Description of studies

Study	Design	Intervention	Length of study	Scale used	Number entered	Number of participants who completed	Primary outcome	Secondary outcomes	Adverse effects reported	Jadad score (for RCTs only)
Davies et al. [18]	Randomized crossover study	Artificial saliva versus pilocarpine	5 weeks: 2 weeks treatment, 1 week washout followed by 2 weeks alternate treatment	0–100 mm VAS to measure symptoms of xerostomia, dysphagia and dysgeusia	63	26	Artificial saliva group: mean change in VAS (xerostomia) + 12 % Pilocarpine group + 46 % p=0.003	–	Yes	1
Davies [17]	Prospective, randomized, open, crossover study	Artificial saliva versus chewing gum	12 days: 5 days treatment, 2 days washout, then 5 days alternate treatment	0–100 mm VAS 0 mm='worst imaginable dryness'. 100 mm='no dryness'	41	26	Mean change in VAS score: Artificial saliva=+ 22.4 mm Chewing gum=+30.1 mm (p=0.49) First-phase differences in treatment p=0.95 Second-phase differences in treatment p=0.34	–	Yes	1
Sweeney et al. [22]	Double-blind, single-phase, placebo-controlled trial	Artificial saliva versus placebo	14 days 7 days with treatment A and then immediate switch to treatment B	VAS clinical examination on severity of dry mouth 0–6	35	26	No statistically significantdifference in effectiveness of both sprays	No significant impact of either spray on oral microflora. No difference in volume of saliva	No	3
Mercadante et al. [19]	Prospective open label study	Pilocarpine	7 days	0–3 severity scale	19	19	Xerostomia improved by 2 points, p<0.0005	–	No	–
Meidell et al. [21]	Prospective study	Acupuncture	5 weeks–10 acupuncture treatments	0–10 cm VAS score for xerostomia, dysphagia, dysarthria 0=no problem or discomfort, 10=severe problems or discomfort	14	8	VAS decreased for xerostomia median 7.5 to 3.3 after 10 treatments p<0.001	VAS decreased for dysphagia 5.7 to 3.6 p<0.01, and dysarthria, 6.2 to 3.5 p<0.01	Yes	–
Rhydholm and Strang [20]	Prospective study	Acupuncture	5 weeks – 10 acupuncture sessions	0–10 cm VAS score	20	15	VAS 8.8 to 4.0 p<0.0001 for xerostomia	Speech problems (n=10) VAS reduced from 8.1 to 3.1 p<0.0001 Dysphagia (n=10) SAS improved from 8.8 to 3.4 p<0.01	Yes	–

considered each treatment had helped their xerostomia with no statistically significant difference between the two interventions. Five participants developed side effects with artificial saliva (commonly unpleasant taste), while seven participants developed side effects with chewing gum (mostly mucosal irritation). Only three participants withdrew because of side effects and they were all associated with chewing gum. Three participants withdrew due to spontaneous improvement in xerostomia. The authors acknowledge the fact that missing data due to patient withdrawal can have a significant impact on the results of the study. In this crossover study, there was no reported carry-over effect of the interventions.

Artificial saliva versus topical placebo

Clinical trial of a mucin-containing oral spray for treatment of xerostomia in hospice patients [22] This was a double-blind, single-phase, placebo-controlled trial comparing Saliva Orthana spray with mucin-free placebo spray with respect to oral symptoms, pathology, salivary flow and microbiology. All but one participant that entered in the study had advanced cancer. The intervention was administered twice a day and as required for 2 weeks.

This study considered xerostomia by VAS score, clinical appearance of oral dryness and salivary flow by measuring salivary volume on the floor of the mouth for 30 seconds using Salivette apparatus. Both interventions helped to relieve the dry mouth with no statistically significant benefit with the active treatment. There was no clinically significant difference between mucin-containing spray and placebo with regards to salivary volume and clinical appearance of xerostomia. Adverse effects and participant withdrawal were not mentioned, though the authors mention that the intervention was not used on a regular basis by some participants and this might have influenced the results.

Pilocarpine alone

The use of pilocarpine in opioid-induced xerostomia [19] This prospective, open label study aimed to determine the role of pilocarpine in reducing xerostomia due to opioid use for the management of pain in people with advanced cancer. All participants were treated with pilocarpine (eye drops 2 % solution) 5 mg by mouth three times a day for a week. Pilocarpine was found to be effective within 24 h of use ($p<0.0005$). No significant side effects were noted with pilocarpine, and no participants withdrew from this study. This small prospective non-randomized open label study concluded that pilocarpine was found to be safe and effective and to have a short onset of activity in almost all the participants. No relationship between opioid dose and degree of xerostomia could be determined.

Acupuncture

Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study [21] This prospective study explored the feasibility of conducting a 5-week, ten-session acupuncture intervention in a hospice and to evaluate its effectiveness. Participants had an equivalent xerostomia VAS score of ≥40 mm to be included. Twenty-four participants agreed to study entry, only 14 started and 8 completed because of clinical deterioration. All participants noted an improvement in their xerostomia, but this only became statistically significant after five sessions ($p<0.001$ after ten sessions). Improvement in dysphagia and dysarthria was also noted in the same time scale. Three participants had side effects, such as a haematoma, but this did not prevent continuing with the treatment.

Acupuncture for patients in hospital-based home care suffering from xerostomia [20] Similar to Meidell and Rasmussmen [21], this prospective study described a 5-week treatment period with ten acupuncture sessions for palliative care patients. Twenty participants entered the study with five withdrawing because of deterioration in health. Improvement in xerostomia was seen over the period of 5 weeks but again only a statistically significant improvement in the VAS scores from five or six treatments ($p<0.0001$). This statistically significant improvement was also seen in dysphagia and speech problems from midpoint of treatment, for those participants who complained of such symptoms. No side effects were documented.

Discussion

This systematic literature review identified three randomized trials and three prospective studies. Saliva Orthana was found to be effective in two randomized studies [17, 18], but a statistically significant difference versus placebo could not be demonstrated in the third randomized study [22]. Pilocarpine was found to be effective in the treatment of xerostomia in two studies [18, 19] but is associated with side effects such as sweating and dizziness. However, no side effects of significant intensity were found with pilocarpine in the prospective study [19] and, as Davies et al. found, these side effects did not stop equal numbers of participants choosing to continue with pilocarpine or Saliva Orthana [18]. Artificial saliva and chewing gum were effective with no statistically significant difference and are associated with some minor side effects [17]. Two prospective studies demonstrated statistically significant improvement (reduction in

xerostomia intensity from 7.5 to 3.3 and 8.8 to 4.0, respectively) in xerostomia with acupuncture but this effect was only seen after five treatments. The authors did not explore for how long this effect was sustained, and the trials did not use sham acupuncture. Those participants receiving treatment tolerated it well, but initially 12 out of the 67 who fulfilled criteria for participation, declined specifically because of fear of needles or no trust in acupuncture. Interestingly, 15 out of the 67 eligible also had a good benefit with saliva substitute [20, 21].

Pilocarpine is a low-cost muscarinic agonist that stimulates salivary flow [23, 24]. Mercadante et al. reported that no patients withdrew because of adverse effects and it was well tolerated [19] compared with Davies et al. reporting that 9 of 38 patients withdrew because of side effects of pilocarpine [18]. Therefore, if commencing pilocarpine, side effects should be monitored in the first week of treatment.

The role of acupuncture for symptom management in cancer has been recently reviewed by Towler et al. with potential for benefit in some symptoms such as fatigue, hot flushes and dyspnoea. They considered acupuncture as a potentially useful adjunct for xerostomia in head and neck cancers undergoing radiotherapy, qualified by the limitations of the methodology of the acupuncture studies [25].

Although there is no primary evidence to support it in advanced cancer patients, simple mouth care may be effective for the management of xerostomia. In the included studies, 7 out of 104 patient's xerostomia spontaneously resolved, leading to withdrawal from the study, and superiority of mucin active ingredient over placebo could not be shown in one study [22]. This may be related to changes in medication or a greater emphasis on basic mouth care. A recent study involving elderly people living in long-term care facilities revealed that regular tooth brushing and use of 4 % saline mouthwash decreased xerostomia and oral tongue plaque, demonstrating the potential for simple measures to provide symptomatic relief [26].

Xerostomia is one of the most common symptoms in cancer patients. In two of the included studies, patients reported a mean equivalent range on a VAS 0–100 mm scale of 32 to 88 [17, 20]. A published letter of response to the authors by our group outlined the burden of this condition and lack of consensus on the management in the Yorkshire region [12]. A consensus report based on a literature review in 2010 recommended that management of xerostomia in cancer patients from salivary gland dysfunction should be individualized. However, this report also highlighted the lack of grade A and B recommendations to support treatment choices [8]. The grade C recommendation of the consensus statement suggests the use of saliva stimulant not only to reduce xerostomia but also to reduce the complications associated with xerostomia by increasing the flow of normal saliva. Similarly, our current review only identified three randomized controlled trials and three prospective studies, highlighting the paucity of evidence to support our management. Management of xerostomia still remains an 'orphan topic in supportive care' [27]. There are several studies assessing interventions in patients with radiotherapy-induced xerostomia (head and neck cancer patients) [28], but only few studies have been performed in advanced cancer patients with xerostomia. A systematic review by Furness et al. considered the effectiveness of topical interventions in xerostomia from heterogenous causes including medication, radiotherapy, chemotherapy, autoimmune disease and infection. They concluded that there was no strong evidence to support the use of topical therapies in the management of xerostomia. However, based on available evidence, they did find that the saliva substitute spray was more effective than aqueous electrolyte spray and chewing appeared to increase the saliva production. This Cochrane review involved a different population of patients, but our recommendations for management are similar [29].

The studies included in this review are small with varying degrees of methodological quality, which was assessed using the Jadad score for RCTs and the STROBE statement for the prospective studies. Out of a possible Jadad score of five, the two studies by Davies [17] and Davies et al. [18] scored only 1 and Sweeney et al. [22] scored 3. However, the process of blinding in these studies would have been limited by the different forms of treatment delivery, i.e. artificial saliva versus chewing gum or pilocarpine. Sweeney et al. were able to blind because of their use of placebo spray. The three prospective studies did show a range in the methodological quality. Both acupuncture studies had limited discussion and analysis on the confounding factors such as xerostomic drugs. Rydholm and Strang [20] and Mercadante et al. [19] did not clearly describe the selection of participants. Mercadante et al. did not discuss limitations of their study. All three prospective studies did not report a reduction in bias with methodological changes in keeping with current recommendations. Conflict of interest statements were not declared in any of the included studies in this review which leaves the possibility of funding bias.

In the absence of evidence for other interventions including good mouth care and acknowledging the limitations of the included studies, we would recommend pilocarpine, artificial saliva sprays and chewing gum for xerostomia in patients with advanced cancer. Acupuncture could be considered but is clearly limited by the treatment length required and access to treatment in comparison with the other treatments described here. As there is little to differentiate between them, treatment decisions should be individualized based on patient preference and side effect profile.

Research in the palliative population is challenging due to high withdrawal rates secondary to deterioration in health. In the included trials, 57 patients withdrew out of a total of 203. Unsurprisingly, there were more withdrawals in trials with a longer duration. The high rates of withdrawal over a short time period highlight the difficulty in conducting primary research in these patients and the need for effective and quick acting treatments of xerostomia. It also may reflect the poor efficacy of the interventions used to treat xerostomia, leading to trial withdrawal.

Patients receiving radiotherapy for head and neck cancers were excluded in the review. Xerostomia can result from both acute and longer term effects of radiotherapy through irradiated tissue fibrosis [30]. More recent studies indicate intensity-modulated radiation therapy (IMRT) and other parotid-sparing techniques result in lower doses of radiation to the oropharyngeal tissues compared with older techniques, resulting in less severe xerostomia [31, 32]. The evidence base for the management of xerostomia in patients received parotid-sparing treatments such as IMRT could prove beneficial for the population in this study and would be an area of future investigation.

Strengths and limitations of the systematic review

Our search strategy was broad and designed in conjunction with the hospital librarian and based on the advanced cancer population. To ensure maximum data collection, a data extraction form was devised and tested a priori by the group. We included use of the Jadad score as a marker for the included randomized controlled trials and the STROBE statement was used when reviewing the prospective studies. Articles were selected independently by two of the authors and cross-referenced. The selected, agreed articles were then reviewed by two authors with a third author available if any area of discrepancy.

Initially, acupuncture was not included in our search strategy but the search was re-run with this included after it was found through references of other articles. There is a possibility of missing data due to unpublished research resulting in publication bias. We are aware from the Clinical Trials Register that a phase II study of a new treatment for xerostomia is in progress (ICTRP identification number: EUCTR2011-000978-53-DK).

We searched only English literature, and this could lead to a publication bias. As highlighted by our initial omission of acupuncture, there is a risk of not considering all interventions used to treat this condition, but it is hoped that this was minimized by our initial scoping search. We recognize that all of the above factors may potentially bias the results of review.

Due to the small number of studies and varying degree of methodological quality, meta-analysis could not be performed and for the same reason we could not assess publication bias.

Conclusion

Xerostomia is a highly prevalent condition, which can result from many of the fundamental treatments we use for palliative care patients. Though there is low quality evidence to support the use of salivary substitutes and stimulants for the condition, pilocarpine, chewing gum, acupuncture and artificial saliva can be considered taking into account a patient's side effect profile and preference. Simple measures such as mouth care, ice cubes and water can also be used though there is no primary research evidence for these interventions in advanced cancer patients. There is further available research in the post-radiotherapy head and neck cancer population which has been excluded from this review but potentially can influence the management of advanced cancer patients in the future. Further randomized controlled trials with larger sample sizes are needed which should include the comparison of basic mouth care to pharmacological measures. Further research in this area will help to improve the quality of life in advanced cancer patients.

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Conflict of interest We declare that we do not have any conflict of interest.

Appendix

Table 3 Excluded literature

Type of studies excluded	Number
Head and neck cancer radiotherapy	195
Non-malignant	10
Flow studies	7
GVHD	5
Mucositis	3
Autoimmune	2
Drug information	3
In vitro studies	1
Guidance and audit	1

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